Genetic counseling: DNA testing for the patient

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Genetic counseling deals with the "human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in the family" (1). Genetic counseling is essentially a communication process—about medical facts, the contribution of heredity to certain conditions, the interpretation of test results, and the options available. It also involves supportive counseling to enable patients to make decisions and to make the best possible adjustment to the presence or risk of genetic disease. Genetic counselors have master's degrees from certified programs and are certified by either the American Board of Medical Genetics or the American Board of Genetic Counseling.

This article reviews several case scenarios in order to highlight some themes and lessons from genetic counseling.

DNA TESTING IN A PRENATAL CASE: CYSTIC FIBROSIS

In recent years, obstetricians have begun offering cystic fibrosis carrier screening to all couples either planning a pregnancy or in the early stages of pregnancy. The incidence of cystic fibrosis in Caucasians is about 1 in 2500. Caucasian men and women with no family history of cystic fibrosis would each have a 1 in 25 chance of being a carrier, i.e., of having one of over 1300 different mutations in the *CFTR* gene. The screening test usually includes analysis for only 23 to 25 of the most common mutations. At this time, sequencing the gene from beginning to end to search for a mutation would be too expensive and time consuming as a screening test.

The decision to undergo carrier screening is a personal one. Some people consider cystic fibrosis a serious disorder appropriate for screening, and others do not. Those who do not may focus on the fact that half of those with the disease survive until the age of 30 or 31, and cystic fibrosis does not involve mental retardation or birth defects. A couple may opt for screening for one or several reasons: because the chance of being a carrier seems high to them, because they would consider prenatal diagnosis if they were shown to be carriers, or because results are usually reassuring. Similarly, those who don't feel the odds of being a carrier are high enough may not be interested in the screening test. Others may not be interested because the cost is not covered by their insurance, the test is imperfect and will not identify all carriers, or they would rather not have the information. Indeed, getting information can provoke anxiety, and some patients prefer not to go down that path.

Some practitioners discourage screening unless the patient plans to pursue prenatal diagnosis. However, my experience has shown that people often change their minds. Some come in with very set ideas about what they would and would not do; until they're faced with a particular circumstance, they may not really know. The point is, options need to be made available.

We will discuss a case in which the woman was screened and found to have mutation G542X *(Figure 1)*. This means that in the 542 amino acid position, glycine has been converted to a stop codon. She is a cystic fibrosis carrier. Since cystic fibrosis is an autosomal recessive disorder, this should not affect her health. However, her husband was subsequently screened, and he was shown to have the most common mutation, ΔF508, a deletion of phenylalanine at position 508. Even though they have different mutations, the mutations are in the same gene. The child now has a 1 in 4 risk of inheriting both mutations and therefore having cystic fibrosis.

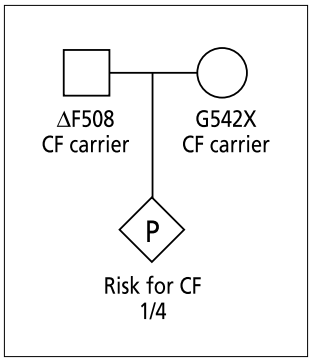

Figure 1. Pedigree of a couple presenting for carrier screening for cystic fibrosis. (See discussion in the text.) Squares represent males, circles represent females, diamonds are used when the gender is unknown or unspecified, and a "P" within the symbol refers to a current pregnancy.

This couple has asked a question and received an answer. What are the next steps? First, prenatal diagnosis should be offered. Even with prenatal diagnosis, the choices are limited: the baby either has the disease or does not have it; the couple will either terminate or not terminate the pregnancy.

Second, the couple should receive information for future pregnancies. The genetic counselor would explain that the 1-in-4 risk occurs in each pregnancy, regardless of how many children they have and how many of the children are already affected. They need information about the different options for prenatal diagnosis and could also consider donor insemination (after screening of the donor) or in vitro fertilization with preimplantation genetic diagnosis. This diagnosis can be accomplished

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by polymerase chain reaction testing of an embryonic cell prior to implantation, analyzing specifically for the mutations identified in the parents. The couple may also choose not to have more children or to pursue adoption. Many more options are available if carrier screening is performed prior to pregnancy rather than during pregnancy.

The test result has implications for the couple's relatives as well. Each sibling of both the husband and the wife has a 50% chance of being a carrier. If the siblings choose to be screened, the laboratory analysis should include the specific mutation found in the family.

Prenatal diagnosis can be performed by chorion villus sampling, generally between 10 and 12 weeks of pregnancy, or amniocentesis, usually at 16 weeks. The risks of these invasive procedures need to be weighed against the risk that the baby has the disorder. In this case, the baby has a 25% chance of having cystic fibrosis, and that is much higher than the <1% risk of procedure-related harm to the pregnancy. Even if the couple desires prenatal diagnosis, it may not be practical or feasible because of lack of resources or because the pregnancy is too advanced.

With prenatal diagnosis, the couple has an opportunity to obtain additional information about the baby—testing for Down syndrome, for example, and other cytogenetic abnormalities. Many people assume that a normal amniocentesis result means that the baby has no genetic problems whatsoever. Of course, that is not true. Since only the gene of interest is tested (in this case, the cystic fibrosis gene), any of the other genes could have mutations that would not be evident from an examination of the number and structure of the chromosomes, as is performed on a cytogenetic evaluation.

Prenatal diagnosis has limitations. Testing may not be 100% accurate, and even with positive results, disease severity cannot be predicted. Knowledge that the mutation is present does not equate with knowledge of how that mutation will affect that child. Even with so-called severe mutations in the cystic fibrosis gene, the disease severity can vary, and much research is focused on possible modifiers of gene expression. The couple would also need information about cystic fibrosis to help them with their decisions. They may or may not wish to have prenatal diagnosis. Some people prefer to know this information so that they can be prepared; others may choose to know with the hope that they will be reassured. The test is not done solely so couples can decide to terminate a pregnancy.

DNA TESTING IN A PEDIATRIC CASE: FRAGILE X

Fragile X is the most common inherited cause of mental retardation. It is similar in incidence to Down syndrome and fetal alcohol syndrome. In adults, the syndrome may be associated with the typical features of a long face, prominent jaw, and large ears; however, molecular testing is required for diagnosis. Within the gene in question, the *FMR-1* gene on the X chromosome, about 30 repeats of a CGG triplet between the promoter and the start codon are normal. Premutation carriers have about 50 to 200 repeats of this sequence; carriers of the full mutation have more than 200 repeats.

Our case study for this disease involves a family of 3 children (*Figure 2*). The first child, a 13-year-old daughter, has no problems; the second child, an 8-year-old boy, has autism with seizures; and the third child, a 3-year-old boy, has developmental delay and is not speaking. At this point, a genetic problem is suspected. Upon testing, fragile X syndrome is diagnosed in both boys. Autistic behavior is very characteristic of fragile X, and in fact fragile X testing is indicated for any child with autism. Delayed speech is typical of the disease as well.

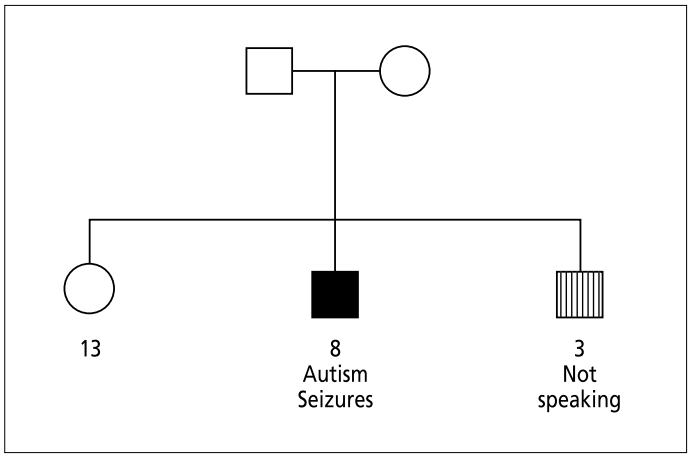

Figure 2. Pedigree of a family diagnosed with fragile X syndrome. Squares represent males and circles represent females.

Having a specific diagnosis—rather than the nonspecific label of mental retardation—is very important. For the two boys, it provides information on prognosis, associated problems, and educational interventions. In addition, a specific diagnosis enables the family to have a support group. They can meet with and learn from other affected families; they can find out about new therapies.

The parents can also use the information in planning to have other children. With two brothers affected with an X-linked condition, the mother must be a carrier. She could have a premutation or a full mutation. The number of triplet repeats tends to expand in subsequent generations when the mutation is passed through a woman; a woman with a premutation, then, may pass on a full mutation. All males who inherit a full mutation will have mental retardation; about half of the females with a full mutation will have mental retardation. Those with the premutation may have some effects as well: Women have an increased frequency of premature menopause, and both men and women, but particularly men, can develop a syndrome of ataxia, tremor, and gait abnormalities after age 60. As a result, we may begin to see fragile X testing in some movement disorder clinics. These parents will need information about their chances of passing on a premutation, passing on a full mutation, and having a child with mental retardation—all of these being different numbers. They will also need information about various reproductive options such as prenatal diagnosis, as described in the previous case example.

The 13-year-old daughter in this scenario has a 50% risk of being a carrier, and she should be tested prior to becoming pregnant. On the mother's side, there are probably other relatives who are carriers. While the family has an obligation to share information about this disorder with their relatives, doing so can be very challenging. A genetic counselor can help the family with this process.

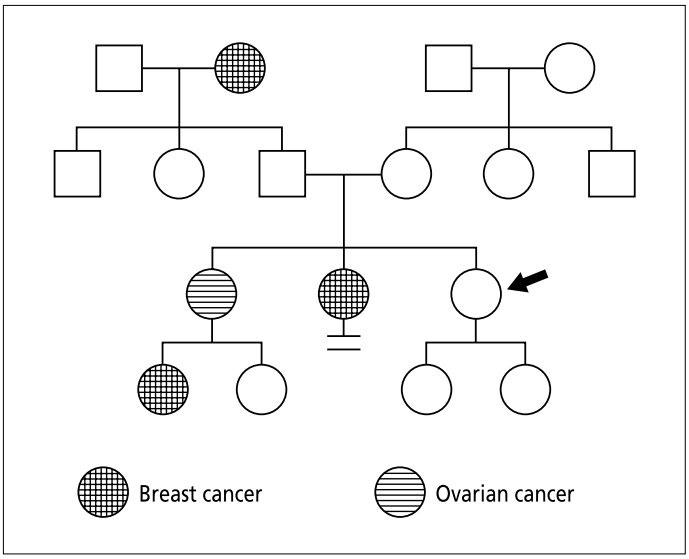

Figure 3. Pedigree of a family with hereditary breast-ovarian cancer. Squares represent males and circles represent females. The woman seeking genetic counseling is indicated by an arrow.

DNA TESTING FOR ADULT-ONSET DISEASES: HEREDITARY BREAST AND OVARIAN CANCER

A subtle difference exists between predictive testing and predisposition testing. The former involves a very penetrant gene: Those who inherit such a gene will develop the disorder if they live long enough. The best example of predictive testing is Huntington disease, an adult-onset autosomal dominant disorder for which a very accurate molecular test is available. On the other hand, predisposition testing refers to testing for a gene that confers a predisposition to a disease. This applies to many cancer genes, including *BRCA1* and *BRCA2*, genes for hereditary breast and ovarian cancer. Mutations in these genes confer an increased risk of cancer (primarily breast and ovarian cancer), although not everyone with a mutation will develop cancer. Because of the many mutations in *BRCA1* and *BRCA2*, the standard test at this time involves sequencing.

A pedigree of our featured family shows multiple relatives with breast or ovarian cancer in a classic pattern of autosomal dominant inheritance *(Figure 3)*. Although cancer appears to skip the second generation, two of the individuals in that generation are male, and men are much less likely than women to develop breast cancer. Note also that the mutation causing breast and ovarian cancer can be passed through a male.

A cancer-free woman in the third generation seeks counseling. Both of her sisters, her grandmother, and one niece have been affected, and she is rightly concerned. Pursuing testing could be beneficial to her. If she has the cancer-predisposition gene mutation, she can pursue increased surveillance and hopefully detect any cancer early. She can also consider chemoprevention and prophylactic surgery. If she does not have the mutation, she can avoid the extra surveillance and follow normal recommendations for screening. She can also use the information for planning: reproductive planning, financial planning, insurance planning, educational and vocational planning. Many people express a strong desire simply to know, one way or another, whether they have inherited a family condition, and they choose to undergo testing for that reason.

An important point is that if this woman is tested without testing anyone else in the family, a negative result may not be interpretable. Her family may have an undetectable mutation or a mutation in a different gene. Therefore, the best way to screen is to begin with a sample from an affected family member. Once a mutation has been documented in that individual, relatives can be screened for that mutation. Otherwise, interpreting negative results is dangerous.

For this patient, receiving a positive result may have drawbacks as well as benefits. A genetic counselor would encourage the patient to consider these before the testing is performed and help her decide whether, on balance, the testing will be helpful. People who test positive may experience paranoia and psychosomatic symptoms, believing that everything is cancer. They are at risk of depression and increased anxiety. They may feel guilty for passing on the gene to their children. Although insurance discrimination and job discrimination are not supposed to happen, there is a chance that they may occur. Information on genetics is very personal; individuals who test positive may have self-esteem issues or feelings of shame. They may be faced with difficult decisions, such as whether or not to have children. Women may have to

Important considerations for genetic testing

Principles

- The gene to analyze—and often the specific mutation to assay—must be determined before testing.
- Not all mutations cause disease.
- Not all mutations are detectable.
- Knowledge of the specific mutation may not necessarily predict disease severity.
- Determining that a mutation is present is not equivalent to diagnosing the presence of disease.

Factors in deciding to test

- The usefulness of the information needs to be determined.
- In some cases, there are no treatment, prevention, or management guidelines for those with a positive test result.
- Knowledge of the result may lead to difficult decisions.
- Carrier or predictive testing is not performed on children unless the results can be used in their clinical management.

Repercussions of testing

- Genetic testing raises confidentiality and privacy issues.
- There is concern about the possibility of job or insurance discrimination.
- DNA testing is highly personal and is threatening for some people. It is often associated with anxiety, fear, and guilt.
- Results have implications for relatives, and people are often ill-equipped to disseminate this information to their family members.
- Family dynamics may be affected—for example, through strained relationships between affected and unaffected relatives and pressure to discuss sensitive matters. Obtaining specimens from relatives may be difficult.
- Previously unknown family relationships such as nonpaternity may be uncovered by family testing.

decide whether to have a mastectomy or oophorectomy. Genetic testing can also strain family relationships. Relatives who did not want to think about breast and ovarian cancer are forced to face up to it—and the timing may not be good for them. They may criticize the one choosing to be tested.

Even receiving normal results can lead to problems, and these are often not considered. Some people experience "survivor guilt"—feeling guilty that they have been spared when others have not. Some may have grown up in a family where everybody has this disease and they believe it to be their fate; a normal test result may take that identity or that crutch away from them. They would no longer have the disease to blame for not going to college or not getting married, for example, and they may begin to regret their choices. Whereas they may have felt that they were "in this together" with other relatives, a normal test result may cause them to feel distant from affected or at-risk relatives. Sometimes negative results lead to unrealistic expectations and false optimism. Some women may stop normal surveillance efforts such as regular mammograms that are appropriate for the general population.

CONCLUSION

Knowledge in the field of genetics is constantly expanding. New genes are being discovered; new mutations are being identified; new tests are being developed. The logistics of DNA testing is often complicated. Because of patents and specialization, some tests are performed at a very limited number of laboratories. There are problems with access, cost, and insurance coverage. Quality control remains a challenge as well. The website www.genetests.org is an excellent resource for clinical and research genetic testing. The site includes up-to-date reviews about selected genetic disorders, as well as links to both clinical and research laboratories that perform tests for specific disorders.

Because of the complexity of genetic testing, the difficult decisions involved, the potential for misinterpretation, the effect on family dynamics, and the emotions that can result, patients and health care professionals need to consider many factors before and during testing (see sidebar). Genetic counselors are trained to assist in this process, providing counseling so that patients can make informed decisions about testing and use the results to their best advantage.

1. Ad Hoc Committee on Genetic Counseling. Genetic counseling. *Am J Hum Genet* 1975;27:240.